

**STABILIZED FORMULATIONS
CONTAINING ANTI-INTERLEUKIN-6
RECEPTOR (IL-6R) ANTIBODIES**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a continuation of U.S. application Ser. No. 16/100,020, filed Aug. 9, 2018, which is a continuation of U.S. application Ser. No. 14/861,565, filed Sep. 22, 2015, now U.S. Pat. No. 10,072,086, which is a continuation of U.S. application Ser. No. 12/986,223, filed Jan. 7, 2011, now U.S. Pat. No. 9,173,880, which claims the benefit under 35 USC 119(e) of U.S. Application No. 61/293,227, filed Jan. 8, 2010, each of which is incorporated herein by reference in its entirety.

REFERENCE TO A SEQUENCE LISTING

[0002] This application includes an electronic sequence listing in a file named "6013US04-Sequence.txt", created on Apr. 8, 2021 and containing 37,549 bytes, which is hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0003] The present invention relates to the field of therapeutic antibody formulations. More specifically, the present invention relates to the field of pharmaceutical formulations comprising a human antibody that specifically binds to human interleukin-6 receptor.

BACKGROUND

[0004] Therapeutic macromolecules (e.g., antibodies) must be formulated in a manner that not only makes the molecules suitable for administration to patients, but also maintains their stability during storage. For example, therapeutic antibodies in liquid solution are prone to degradation, aggregation and/or undesired chemical modifications unless the solution is formulated properly. The stability of an antibody in liquid formulation depends not only on the kinds of excipients used in the formulation, but also on the amounts and proportions of the excipients relative to one another. Furthermore, other considerations aside from stability must be taken into account when preparing a liquid antibody formulation. Examples of such additional considerations include the viscosity of the solution and the concentration of antibody that can be accommodated by a given formulation. Thus, when formulating a therapeutic antibody, great care must be taken to arrive at a formulation that remains stable, contains an adequate concentration of antibody, and possesses a suitable viscosity as well as other properties which enable the formulation to be conveniently administered to patients.

[0005] Antibodies to the human interleukin-6 receptor (hIL-6R) are one example of a therapeutically relevant macromolecule that requires proper formulation. Anti-hIL-6R antibodies are clinically useful for the treatment and/or prevention of diseases such as rheumatoid arthritis, ankylosing spondylitis, and other conditions. Exemplary anti-IL-6R antibodies are described, inter alia, in U.S. Pat. Nos. 7,582,298; 6,410,691; 5,817,790; 5,795,695; and 6,670,373. A particularly important anti-hIL-6R antibody with great therapeutic potential is the antibody referred to in U.S. Pat. No. 7,582,298 as VQ8F11-21 (also referred to herein as "mAb1").

[0006] Although anti-hIL-6R antibodies are known, there remains a need in the art for novel pharmaceutical formulations comprising anti-hIL-6R antibodies which are sufficiently stable and also suitable for administration to patients.

BRIEF SUMMARY OF THE INVENTION

[0007] The present invention satisfies the aforementioned need by providing pharmaceutical formulations comprising a human antibody that specifically binds to human interleukin-6 receptor (hIL-6R). The formulations of the invention may comprise excipients in addition to the anti-hIL-6R antibody. For example, in certain embodiments, the formulation may comprise (i) a human antibody that specifically binds to hIL-6R; (ii) at least one amino acid; and (iii) at least one carbohydrate. The amino acid can be, e.g., histidine and/or arginine. The carbohydrate can be a sugar such as, e.g., sucrose, glucose, mannitol, lactose or trehalose.

[0008] According to certain embodiments of the present invention, the formulation further comprises a non-ionic surfactant. The non-ionic surfactant can be, e.g., polysorbate 20, polysorbate 80, polyoxyethylene sorbitan monooleate, polyethylene glycol, etc.

[0009] The antibody contained within the pharmaceutical formulations of the present invention can be any antibody which specifically binds to hIL-6R. Exemplary antibodies that may be contained within the formulations of the invention are antibodies comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein the HCVR comprises a heavy chain complementary determining region (HCDR) 1 having the amino acid sequence of SEQ ID NO: 20, a HCDR2 having the amino acid sequence of SEQ ID NO:22, and a HCDR3 having the amino acid sequence of SEQ ID NO:24; and wherein the LCVR comprises a light chain complementary determining region (LCDR) 1 having the amino acid sequence of SEQ ID NO: 28, a LCDR2 having the amino acid sequence of SEQ ID NO:30, and a LCDR3 having the amino acid sequence of SEQ ID NO:32. In certain embodiments, the antibody contained within the formulations of the present invention are antibodies comprising a HCVR having the amino acid sequence of SEQ ID NO:18 and a LCVR having the amino acid sequence of SEQ ID NO:26.

[0010] The antibody formulations of the present invention may be contained within any suitable container useful for storing pharmaceutical formulations. Examples of such suitable containers include, e.g., glass or plastic vials, syringes and cartridges. The container may be clear or opaque (e.g., amber colored).

[0011] According to certain aspects of the present invention, the pharmaceutical formulations remain relatively stable following storage for several days, months or years at a given temperature. For example, in certain exemplary embodiments of the present invention, a high percentage of the antibody (e.g., 90%, 95%, 96% or more) is maintained in its native form following at least 3, 6, 9 or more months of storage. The percentage of native form of the antibody may be measured, e.g., by SE-HPLC, or by any other method known in the art. The storage temperature at which stability of the antibody is maintained can be, e.g., -80° C., -40° C., -20° C., 0° C., 5° C., 25° C., 45° C., or higher.

[0012] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.